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ScienceDirect
Autoimmunity Reviews 7 (2008) 487–490
AUTOIMMUNITY REVIEWS
www.elsevier.com/locate/autrev

Modulation of human dendritic cell maturation and function by natural IgG antibodies

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Available online 7 May 2008

Abstract

Dendritic cells (DCs) are professional antigen-presenting cells, which have a central role in the initiation of primary immune responses and in maintaining immune tolerance. The functions of DCs can be regulated both by environmental signals as well as signals delivered by endogenous molecules. Recently we have examined regulation of human DCs by B cells via natural IgG antibodies. Natural antibodies (NAbs) are defined as antibodies that circulate in normal individuals in the absence of deliberate immunization or microbial aggression. We demonstrate that the differentiation of DCs is severely impaired in primary immunodeficient patients such as X-linked agammaglobulinemia (XLA) and common variable immunodeficiency (CVID) at least in part due to the deficiency of circulating NAbs. Further, we show that NAbs are able to restore normal phenotypes of DCs from patients with XLA and CVID. Our results suggest that B cells promote bystander DC development through NAbs and the interaction between NAbs and DCs may play a role in steady-state migration of DCs.

Keywords: Natural IgG antibodies; Dendritic cells; Intravenous immunoglobulin; X-linked agammaglobulinemia; Common variable immunodeficiency

Contents

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doi:10.1016/j.autrev.2008.04.014

1. Introduction

Dendritic cells (DCs) are professional antigen-presenting cells that are specialized in the antigen recognition, uptake and their transport from peripheral tissues to the lymphoid organs [1]. Because of their capacity to stimulate naive T cells, DCs have a central role in the initiation of primary immune responses. The central role of DCs in regulating the quality of immune responses is linked to the ability of these cells to modify their properties in response to variety of signals they receive [2]. In general, DCs switch from an immature state, in which they are efficient at antigen capture but are poor stimulators of T cells, into a mature and activated state, in which they are potent T-cell activators. Maturation of DCs involves multiple alterations, including changes in antigen processing/presentation and expression of MHC molecules, co-stimulatory molecules, cytokines and chemokines, which affect their ability to attract and regulate the differentiation and activation of T cells. The secretion of DC-derived immunoregulatory cytokines plays a crucial role in the cascade of events occurring during the priming of naive T cells [3].

2. Signals that regulate dendritic cell maturation and functions

The functions of DCs can be regulated both by environmental signals as well as by signals delivered by endogenous molecules [3]. Thus, DCs are equipped with several pathogen recognition motifs i.e., 'pattern-recognition receptors' (PRR) such as TLRs, Nod-like receptors and membrane-associated C-type lectins (CLRs), interaction of which with pathogen-associated molecular patterns (PAMPs) can modulate the production of inflammatory cytokines, phagocytosis, intracellular routing of antigen, release of oxidative species and DC maturation and the subsequent development of adaptive immunity [4,5]. Indirectly, infection-induced signals such as cytokines and molecules released by dying cells can also influence DCs behavior.

Accumulating evidence indicate that both T and B cells have a profound regulatory effect on the functions of DC *in vitro* and *in vivo*. Thus, in addition to providing programming for T-cell differentiation and polarization, DCs themselves undergo 'education' upon receiving reciprocal signaling from T-cell molecules including CD40L, CD28, CTLA-4 and LAG-3 [3,6]. However, recent results suggest that the outcome of interactions with T cells that affect DCs will depend on the properties of the specific T cells involved [6]. Indeed, CD4+CD25+ regulatory T-cell subsets are shown to inhibit the expression of co-stimulatory molecules and T-cell stimulatory capacities of DCs and thus of therapeutic importance [7–16].

B cells can influence the polarization of T-cell responses mediated by DCs. Indeed, DCs from B cell-deprived animals have an impaired capacity to induce Ag-specific differentiation of IL-4-secreting T cells [17,18]. Therefore, B cells may directly, or indirectly, favor the development of Th2-type cells that provide helper activity for immunoglobulin synthesis, thereby promoting their own effector functions. B cells may also actively create a lymphoid microenvironment via cytokines and chemokines that promote their interaction with other cells in orchestrating efficient IgG responses by a constant cross-talk with DC and T cells [19–22].

3. Regulation of human dendritic cell functions by natural IgG

Recently we have examined regulation of human DCs by B cells via natural IgG antibodies. Natural antibodies (NAbs) are defined as antibodies that circulate in normal individuals in the absence of deliberate immunization or microbial aggression [23]. NAbs are the products of germ-line Ig gene expression in B cells that are positively selected during ontogeny [24,25]. The majority of NAbs exhibit autoreactivity and are proposed to participate in the maintenance of immune homeostasis under physiological conditions [26,27].

To address the role of natural IgG antibodies in regulating dynamic immune equilibrium via interaction with DCs, we first examined the status of DCs in patients with primary immunodeficiencies who lack circulating antibodies and thus lack natural IgG. We thus resorted to patients with common variable immunodeficiency (CVID) and with X-linked agammaglobulinemia (XLA). CVID is a heterogeneous disorder that is associated with low serum-immunoglobulin concentrations, defective specific-antibody production and an increased susceptibility to bacterial infections of the